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Brønsted acid catalysis is an emerging area of organocatalysis. The small and labile nature of an acidic hydrogen atom and its interaction with substrates containing basic functional groups allows for the preparation of diverse compounds. When the substrate consists of an electrophile and nucleophile in its structural make-up, the bifunctional nature of a Brønsted acid is an attractive synthetic feature for intramolecular cyclization reactions to form heterocycles.

Heterocycles are cyclic compounds containing at least one non-carbon atom, typically oxygen, nitrogen, or sulfur; and are ubiquitous frameworks in both naturally occurring and pharmaceutical compounds that are bioactive. Lactones are cyclic esters derived from aliphatic hydroxy acids and are a key structural framework in many natural products that exhibit a wide range of biological activity, with five- and six-membered ring lactones being the most common. Novel synthetic approaches for their preparation are necessary to readily access these compounds.

The work described in this thesis provides a novel application of organocatalysis for the synthesis of six-membered ring lactones. The synthesis is carried out by activating hydroxynitriles via a bifunctional Brønsted acid to drive an intramolecular cyclization reaction, generating the desired functionalized lactones. This project contributes to the research scope of utilizing nitriles as versatile building blocks in organic synthesis.

A NOVEL APPLICATION OF ORGANOCATALYSIS FOR THE
SYNTHESIS OF SIX-MEMBERED RING LACTONES

by

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Approved by

Committee Chair

APPROVAL PAGE

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CHAPTER I

INTRODUCTION

1.1 Organocatalysis

Organocatalysis involves the use of metal-free, small organic molecules, predominantly composed of carbon, hydrogen, oxygen, nitrogen, sulfur and phosphorus, to catalyze organic transformations. A variety of carbon-carbon and carbon-heteroatom bond-forming reactions can be carried out using organocatalysis. One of the earliest uses of small organic molecules behaving as catalysts include the works of Emil Knoevenagel. In 1896, Knoevenagel carried out the reaction of benzaldehyde (**1**) with ethyl acetoacetate (**2**) at 0 °C using piperidine (**3**) as the catalyst, and obtained ethyl benzylidene acetoacetate (**4**) as the sole product (Figure 1)¹. This reaction, known as the Knoevenagel condensation, demonstrated that primary and secondary amines can catalyze the aldol condensation of β -ketoesters or malonates with aldehydes or ketones to afford α,β -unsaturated compounds.

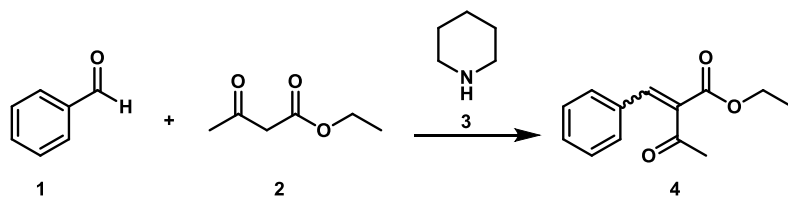


Figure 1. Knoevenagel Condensation

Inspired by the work of Knoevenagel, the proline-catalyzed intramolecular asymmetric aldol reaction of triketones (Hajos-Parrish reaction) was independently reported by two industrial research groups, Hoffmann-LaRoche² and Schering AG³, in the early 1970's. The bicyclic product of this reaction is an important precursor for the synthesis of steroids and other enantiomerically pure complex molecules. The Hajos-Parrish reaction was a key development in organocatalysis for the functionalization of ketones and is one of the earliest enantioselectively catalyzed reactions of practical use in synthetic organic chemistry (Figure 2). Despite the utility of this reaction and other discoveries during this time, transformations using small organic molecules as catalysts were viewed as a unique and isolated synthetic tool; rather than an integral part of a larger, interconnected field.

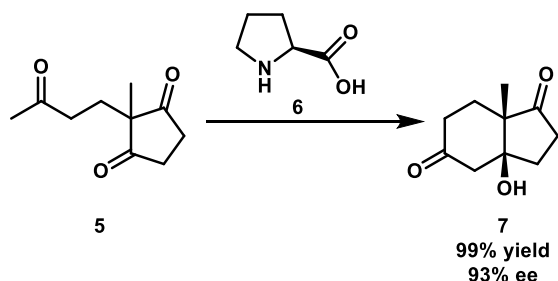


Figure 2. Proline-Catalyzed Intramolecular Aldol Reaction

In 2000, List, Lerner and Barbas⁴ were the first to report proline-catalyzed enantioselective intermolecular aldol reactions between acetone (**8**) and a variety of aldehydes (**9**) to furnish the desired products (**10**) with moderate to good yields and enantioselectivities (Figure 3). Mechanistic studies^{5, 6} showed that L-proline catalyzes the aldol reaction according to an enamine mechanism, behaving similarly to the Type I

aldolase enzyme that nature uses to catalyze stereoselective aldol reactions for the biosynthesis of carbohydrates (Figure 4). The catalytic principle of forming an enamine intermediate has proven to be a general strategy for a wide range of transformations involving carbonyl compounds. Subsequently, variants of the proline-catalyzed aldol reaction have been explored with Michael additions^{7, 8}, Mannich reactions^{9, 10}, α -functionalization of aldehydes and ketones such as amination^{11, 12} and alkylation¹³.

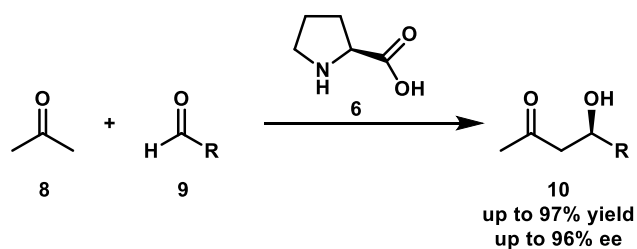


Figure 3. Proline-Catalyzed Intermolecular Aldol Reaction

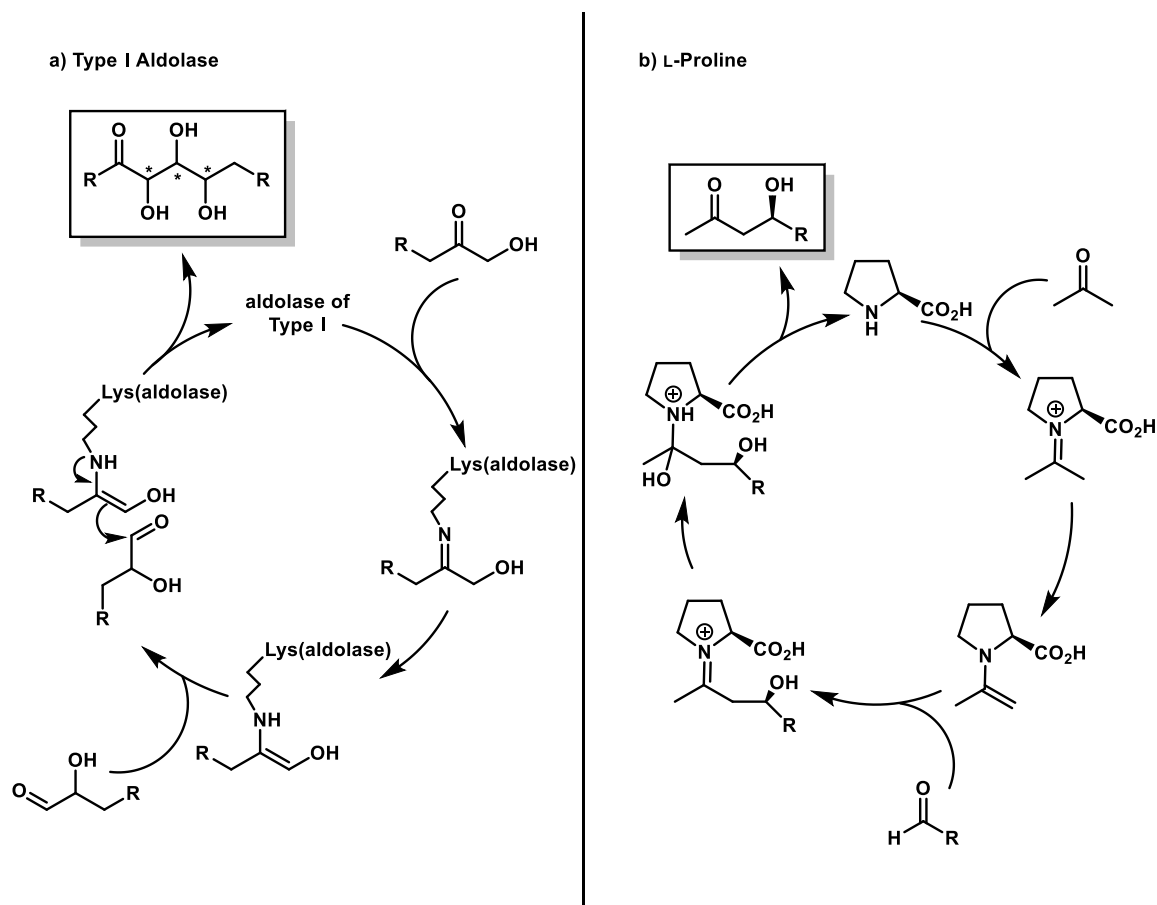


Figure 4. Catalytic Cycles of the Intermolecular Aldol Reaction

The work of List *et. al.*⁴ showed that small organic molecules could catalyze the same chemical reactions as large enzymes with high enantioselectivity, broadening the applicability of organocatalysis in synthetic chemistry. This discovery paved the way to designing organocatalysts and predicting their behavior; thereby, launching organocatalysis as an independent branch of organic synthesis, complementary to enzymatic and metallic catalysis.

The rapid growth and adoption of organocatalysis over the past two decades can be attributed to its many benefits as a synthetic tool. In general, organocatalysts are low

in toxicity, robust and environmentally friendly. They are generally inexpensive to prepare and commercially accessible. Moreover, the reactions are frequently carried-out in a metal-free environment and under mild conditions. Thus, organocatalytic methods are especially attractive for the preparation of compounds that do not tolerate metal contamination, such as pharmaceuticals¹⁴. This feature has made the field very interesting from the industrial perspective, as removal of impurities related to toxic metal catalysts is avoided.

1.2 Brønsted Acid Catalysis

Organocatalysts can be classified by their chemical nature - Lewis acid, Lewis base, Brønsted acid, or Brønsted base. They interact with a substrate through different activation modes to form new C-C, C-H and C-X (X = heteroatom) bonds, accelerating chemical transformations with controlled selectivity. Some are also designed to be bifunctional, capable of activating both nucleophiles and electrophiles.

Brønsted acid catalysis is an emerging area of organocatalysis. The small and labile nature of an acidic hydrogen atom and its interaction with substrates containing Lewis basic functional groups allows for the preparation of diverse compounds. Brønsted acid catalysts can interact with a substrate by two different modes, depending on the degree of proton transfer in the transition state (Figure 5). In hydrogen bonding catalysis, the catalyst serves as a hydrogen bond donor (H-X) toward an electronegative hydrogen bond acceptor (Y). In Brønsted acid catalysis, the catalyst is strong enough to protonate the substrate, forming ion-pairs as intermediates. Catalysts that promote direct protonation are often referred to as stronger Brønsted acids. Discrimination between

these two distinct modes is difficult and computational studies of the transition state are required to differentiate the two activation modes¹⁵.

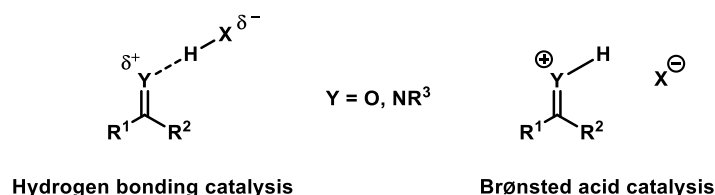


Figure 5. Activation Modes

Chiral Lewis acid catalysts, the combination of a metal-centered Lewis acid and a chiral ligand, have been extensively investigated and are well-known to be efficient electrophilic activators of carbonyl compounds. Recently, Brønsted acids have attracted much attention as suitable chiral catalysts. The ability to activate electrophiles with hydrogen bonding or protonation bears a direct analogy to Lewis activation. Instead of using metals to coordinate the lone pair of a carbonyl oxygen atom, interactions with the hydrogen atom promotes activation and generates a chiral environment around the electrophilic species. The pioneering studies of the groups of Akiyama and Terada in 2004 demonstrated the use of chiral BINOL phosphates as powerful Brønsted acid catalysts in asymmetric Mannich -type reactions^{16, 17}. Since then, Brønsted acids have been applied to a variety of reactions for enantioselective C-C and C-X bond formations. Typical chiral Brønsted acids are based on bifunctional thiourea (**11**), TADDOL (**12**), or BINOL-derived phosphoric acid (**13**) (Figure 6)¹⁸. However, numerous variations of mostly BINOL-derived phosphoric acids have been developed.

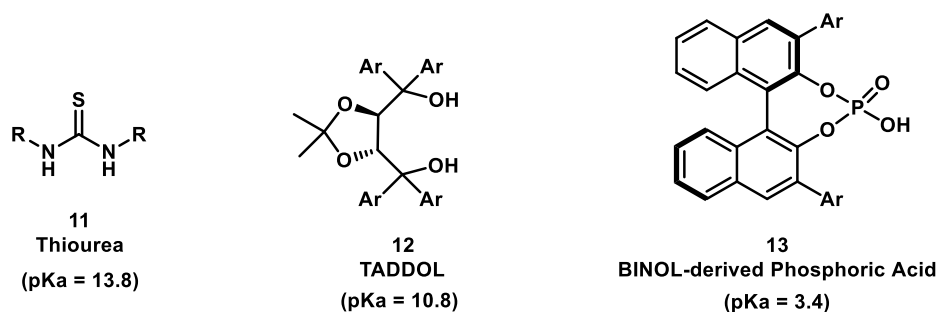


Figure 6. Common Chiral Brønsted Acid Catalysts

One type of hydrogen bonding involves electrophilic activation of carbonyl compounds toward nucleophilic attack. The carbonyl functional group is polar because oxygen is more electronegative than carbon, having a greater tendency to pull the π electrons toward itself. As a result, the carbon atom is electron-deficient and prone to nucleophilic attack. As a hydrogen atom of a Brønsted acid interacts with the oxygen atom of a carbonyl or the nitrogen atom of an imine, the electrophilic character of the carbon atom is enhanced, increasing its propensity towards nucleophilic attack (Figure 7).

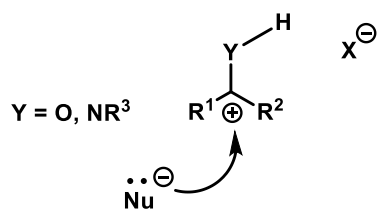


Figure 7. Electrophilic Activation of Carbonyl or Imine Compounds

1.3 Heterocyclic Compounds

When the substrate consists of an electrophile and nucleophile in its structural make-up, the bifunctionality of a Brønsted acid is an attractive synthetic feature for intramolecular cyclization reactions to form heterocycles. Heterocycles are cyclic compounds containing at least one non-carbon atom, typically oxygen, nitrogen, or sulfur. About half of the known organic compounds contain at least one heterocyclic component¹⁹. Heterocycles are ubiquitous frameworks in both naturally occurring and pharmaceutical compounds that are bioactive. The type and size of ring structures, coupled with the functional groups bonded to the core scaffold, contribute to the versatility and physiological properties of heterocycles.

Lactones are cyclic esters derived from aliphatic hydroxy acids and constitute one of the most important classes of compounds in organic chemistry. They are largely responsible for the flavor and fragrance of fruits and flowers; and their odorant properties are used in the essential oils and fine perfumery industry. Lactones are a key structural framework in many natural products that exhibit a wide range of biological activity, with five- and six-membered ring lactones being the most common²⁰. For example, camptothecin (**14**) (Figure 8) is a quinoline alkaloid derived from the Chinese tree *Camptotheca acuminata* that was identified in an anti-cancer drug discovery screen in the 1960s. It has anti-cancer activity against a large range of tumors by binding to DNA topoisomerase I and, thereby, inhibiting its activity²¹. The semi-synthetic analogue topotecan (**15**) (Figure 8) has been FDA-approved for treating ovarian, lung and colon cancer²². Another interesting natural compound with the lactone backbone is lovastatin

(**16**) (Figure 8). It inhibits 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase to lower cholesterol. Lovastatin is a natural product in oyster mushrooms (*Pleurotus ostreatus*) and red yeast rice (rice fermented by *Monascus*)²³.

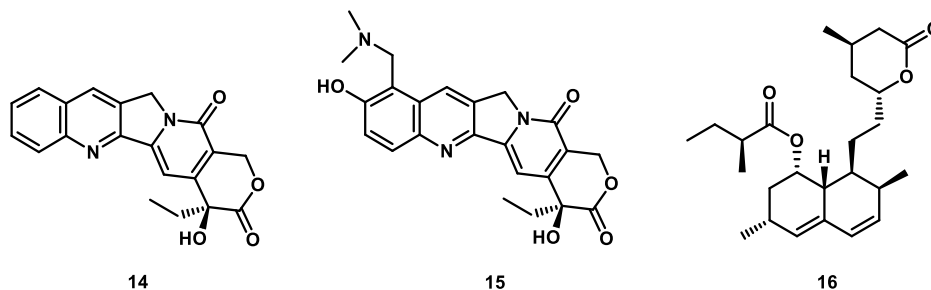


Figure 8. Natural Products Containing the Lactone Motif

Due to the industrial applications and medicinal benefits of lactones, novel synthetic approaches for their preparation are necessary to readily access these compounds.

1.4 Research Objective

The reactivity of nitriles is similar to carbonyl compounds due to the polarity of the carbon-nitrogen triple bond. The resonance structure of nitriles shows that the carbon atom is electrophilic, making nitriles prone to nucleophilic attack (Figure 9). The lone pair of electrons on the nitrogen atom are contained in a *sp*-hybridized orbital, making the nitrogen atom a weakly basic site. Interaction with an acid enhances the polarization, making the carbon atom a better electrophile with increased susceptibility to nucleophilic attack.

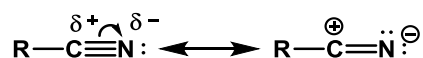


Figure 9. Resonance Structure of the Nitrile Functional Group

The overall goal of this project is to synthesize six-membered ring lactones by activating hydroxynitriles (a nitrile containing a hydroxy substituent) via a Brønsted acid. The hypothesis is that a Brønsted acid will behave as a bifunctional agent, activating both the cyano and hydroxy functional groups present in the substrate, resulting in an intramolecular cyclization reaction. The proposed transition state suggests that the acidic proton of the agent (e.g. sulfonic acid) coordinates with the nitrogen atom of the nitrile and the basic oxygen coordinates with the hydrogen atom of the hydroxyl group (Figure 10). The electrophilic carbon atom of the nitrile group can readily undergo nucleophilic attack by the oxygen atom of the hydroxyl group.

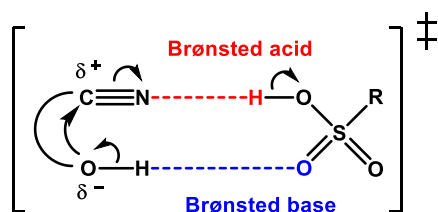


Figure 10. Proposed Transition State

Because the cyano group can undergo various chemical transformations, nitriles are important intermediates in organic synthesis (Figure 11). Utilization of nitriles as a synthetic substrate for the preparation of heterocycles is a well-studied field of research. Several reports provide an extensive review on this subject^{24, 25}. However, much of the research is limited to the construction of five- and six-membered ring structures that are

derivatives of furan, thiophene, pyrrole, pyrazole, pyridine, and pyridazine. This project will expand the research scope of utilizing nitriles as versatile starting materials in organic synthesis.

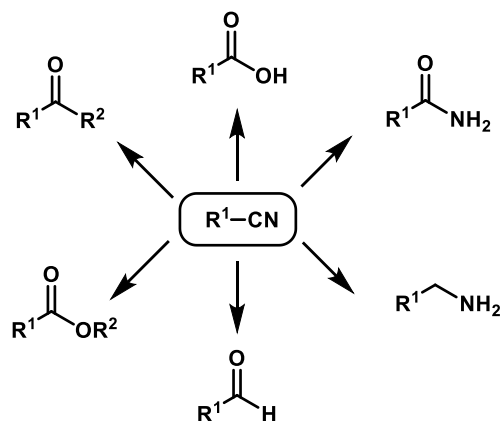


Figure 11. Chemical Transformations of the Nitrile Functional Group

CHAPTER II

SYNTHESIS OF SIX-MEMBERED RING LACTONES

2.1 Common Routes for the Synthesis of δ -Lactones

The δ -lactone moiety (a six-membered ring) is a common structural subunit present in many natural products. The biological significance of δ -lactones, along with their synthetic utility, is of keen interest among synthetic chemists and has led to the development of a variety of methods for their synthesis. Common synthetic methods include lactonization of δ -hydroxy acids or δ -hydroxy acid derivatives (**17**), halolactonization of olefinic acids (**18**), oxidative lactonization of diols (**19**), Baeyer-Villiger oxidation of cyclopentanones (**20**), and oxidation of lactols (**21**) (Figure 12)²⁶.

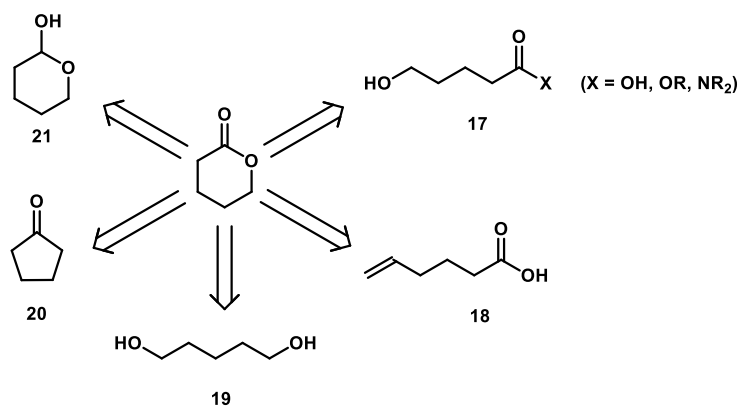


Figure 12. Common Strategies for the Synthesis of δ -Lactones

2.2 Previous Studies on Using Hydroxynitriles to Synthesize Lactones

Examples of using nitriles for the preparation of lactones is based on the Pinner reaction; but, are not common in the literature. The Pinner reaction involves the condensation of nitrile (**22**) with alcohol (**23**) under anhydrous conditions in the presence of hydrogen chloride to afford an imino ether (**24**); the imino ether, generally not very stable, can undergo rapid hydrolysis in the presence of an acid and water to form ester (**25**) (Figure 13)²⁷. If the nitrile and alcohol are treated with aqueous hydrochloric acid, the ester is formed directly. Moreover, a hydroxynitrile could undergo an intramolecular Pinner cyclization to generate a lactone.

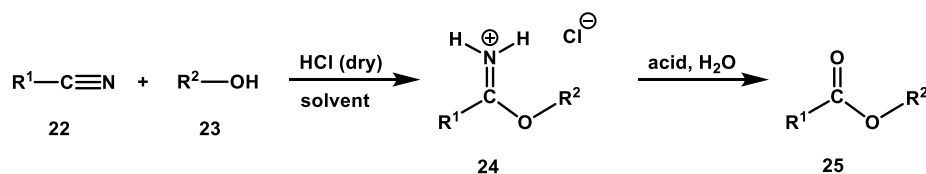


Figure 13. Pinner Reaction

Kula *et al.* developed a method to produce enantiomerically pure (*R*)- γ -decalactone, a lactone commonly used in fruit and dairy flavors²⁸. The reaction involved 4-hydroxydecanitrile (**26**) undergoing an Pinner cyclization in the presence of dilute HCl to afford (*R*)- γ -decalactone (**27**) in quantitative yield (Figure 14a). Another study demonstrated that a heterogenous catalyst (acidic cation exchange resin) in water at 135 °C efficiently promoted the Pinner cyclization/hydrolysis reaction sequence of hydroxynitrile (**28**), generating the cyclic imidate (**29**), to furnish γ -lactone (**30**) with a 96% yield (Figure 14b)²⁹. A synthetic method for the preparation of 5,6-dihydropyran-

2-ones (**32**) via acid-promoted reactions of 5-hydroxypent-2-enitriles (**31**) was developed by Zhang *et al.* (Figure 14c)³⁰. By varying the substituents attached on different positions of the substrate, diversely substituted 5,6- dihydropyran-2-ones, structural scaffold frequently found in both natural products and pharmaceutical agents, were obtained with moderate to good yields.

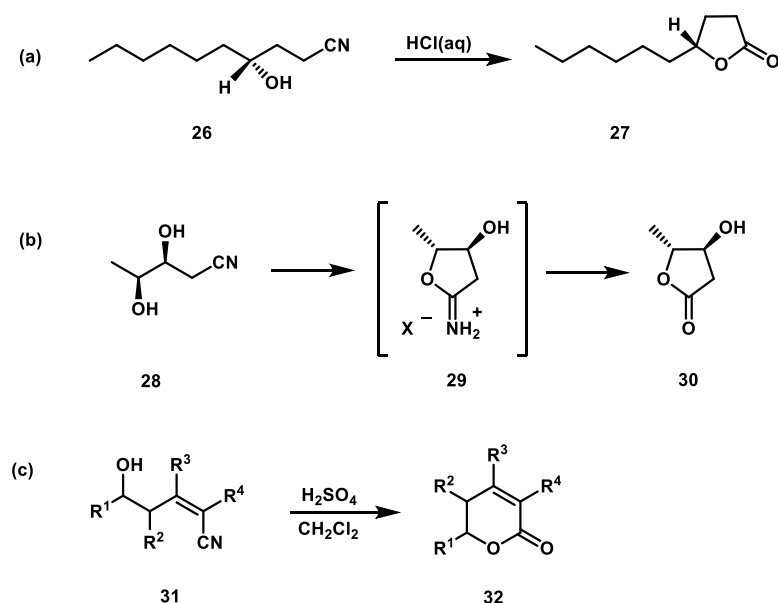


Figure 14. Examples of Using Hydroxynitriles to Synthesize Lactones

2.3 A Novel Methodology for the Synthesis of δ -Lactones

A novel application of organocatalysis for the synthesis of δ -lactones was developed to expand their synthetic utility. The proposed methodology is illustrated in Figure 15, with the novelty of the synthetic protocol highlighted in red font. First, reduction of alkene (**33**) with sodium borohydride generates dinitrile (**34**). 3-Bromo-1-propanol (**35**) is protected with a silyl ether group to prepare compound (**36**). Compound

(**34**) can undergo alkylation with compound (**36**) via an S_N2 reaction to produce compound (**37**). The removal of the protecting group yields alcohol (**38**), which can cyclize via electrophilic activation of one of the nitriles using a Brønsted acid, giving the iminolactone (**39**). The final step of the pathway is the conversion of (**39**) to lactone (**40**) via hydrolysis.

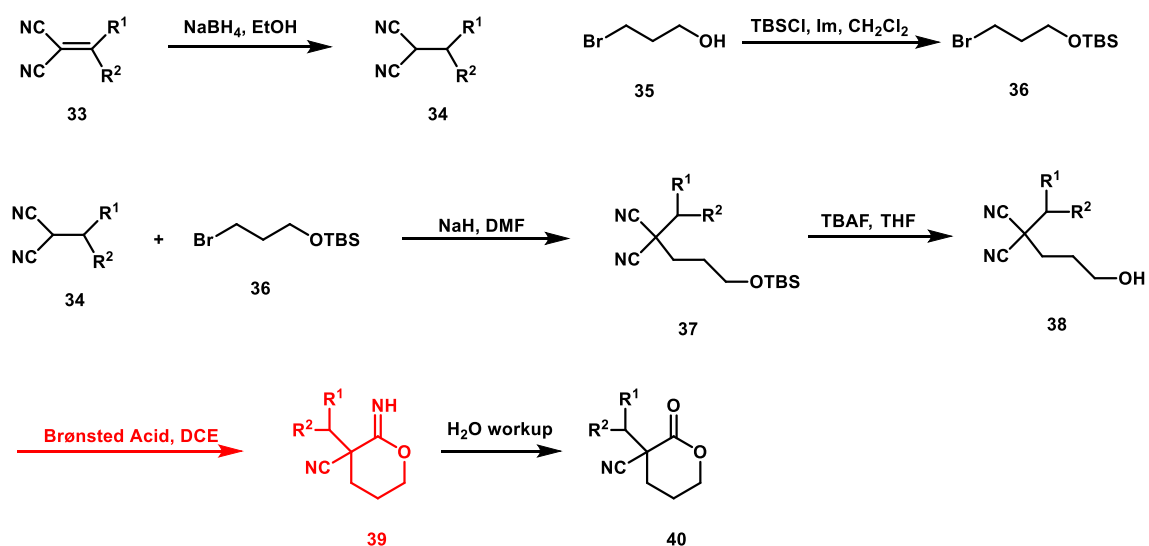


Figure 15. Proposed Synthetic Methodology

Due to the presence of two nitrile groups, this methodology could generate a wider range of lactones than the previously described Pinner cyclization methods. Cyclization of one nitrile group could furnish the desired lactone, while the other nitrile could undergo further chemical transformations to generate functionalized lactones (Figure 11). The chemoselectivity of a dinitrile to furnish various lactones makes this synthetic strategy a unique and novel approach to constructing lactones.

2.4 Results and Discussion

2.4.1 Synthesis of Substrates

An efficient and convenient method for the synthesis of monosubstituted malononitrile was developed to selectively control its formation over the undesired disubstituted product that is generated from over alkylation^{31, 32}. The first step is a Knoevenagel condensation between malononitrile (**41**) and a ketone or an aldehyde (**42**); the intermediate dicyanoalkene (**43**) is reduced in a second step to afford the desired monosubstituted malononitrile (**44**) (Figure 16).

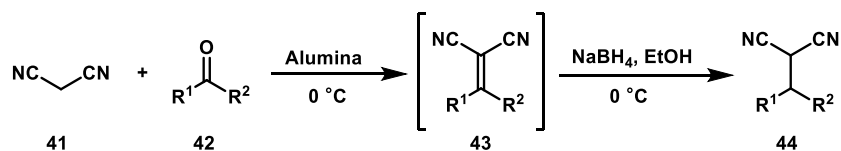


Figure 16. Reductive Alkylation of Malononitrile

Benzyl malononitrile and isopropyl malononitrile were selected as the substrates to screen the reaction scheme's ability to produce the desired lactones. The dicyanoalkene is commercially available from Sigma-Aldrich with 98% purity. Thus, only the reduction step is necessary to synthesize the starting materials. The reductive alkylation of compounds (**45**) and (**47**) furnished benzyl malononitrile (**46**) and isopropyl malononitrile (**48**) with yields of 93% and 54%, respectively (Figure 17).

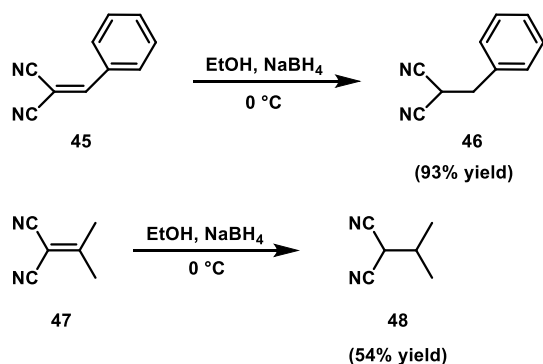


Figure 17. Reductive Alkylation of Compounds 45 and 47

The gas chromatogram of the crude product for (**48**) showed a peak at a retention time of 13.790 minutes (Figure 18). To minimize the formation of the by-product, the reaction was conducted at -10 °C and monitored by TLC. Based on no detection of the starting material on the TLC plate, the reaction was quenched after 3 hours. Unfortunately, the by-product was still generated as a 1:4 mixture with (**48**). The by-product was isolated for further analysis. It was a yellow precipitate and the ¹H NMR spectrum showed some indication that the nitrile functional group may have reduced to a primary amine.

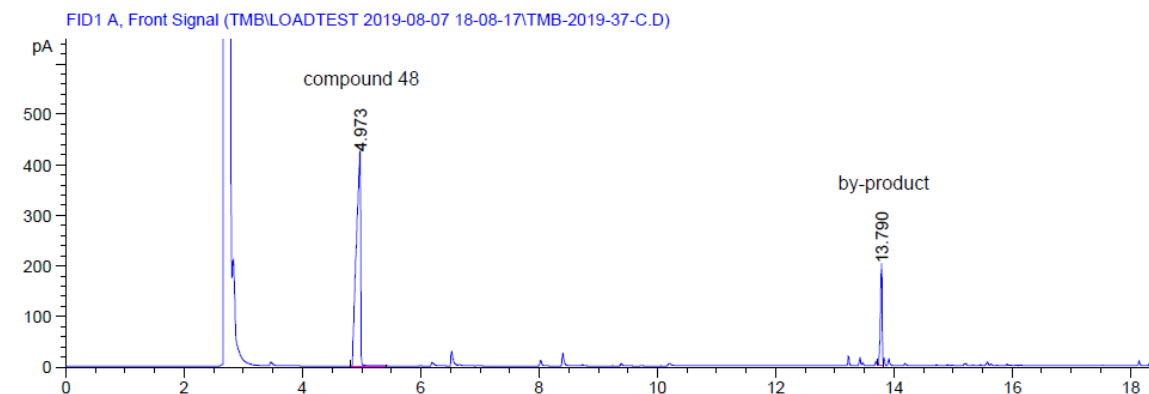


Figure 18. Gas Chromatogram of the Crude Product for Compound 48

2.4.2 Synthesis of Alkylating Agent

Synthesis of the alkylating agent involved the installation of a silyl ether protecting group via chemical modification of the hydroxyl group to achieve chemoselectivity in the subsequent reaction. 3-Bromo-1-propanol (**49**) was protected with *tert*-butyldimethylsilyl chloride (TBSCl) in the presence of imidazole (Im) and dichloromethane (CH₂Cl₂) to afford compound (**50**) in quantitative yield (Figure 19).

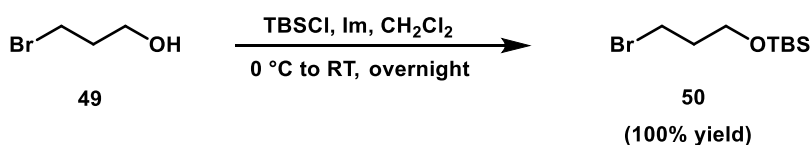


Figure 19. Silyl Ether Protection of Compound 49

Compound (**49**) serves as a nucleophile and attacks the electrophilic silicon atom of TBSCl, generating a protonated silyl ether intermediate. Then imidazole deprotonates the intermediate, forming (**50**). The proposed mechanism for this reaction is depicted in Figure 20.

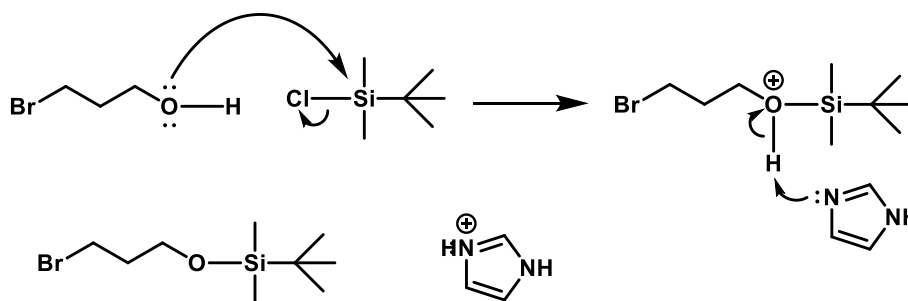


Figure 20. Proposed Mechanism for the Protection Reaction

2.4.3 Alkylation and Deprotection

Alkylation of compounds (**46**) and (**48**) was conducted using sodium hydride (NaH) in dimethylformamide (DMF) to form compounds (**51**) and (**52**) in 40% and 47% yields, respectively (Figure 21).

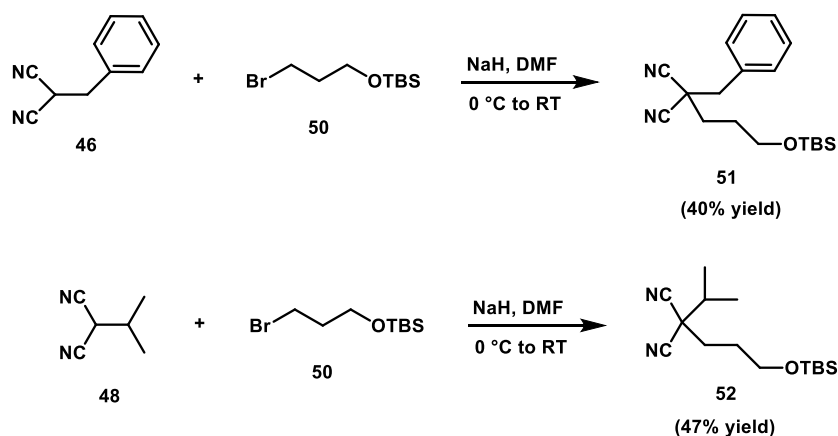


Figure 21. Alkylation of Compounds 46 and 48

The hydrogen between the two electron withdrawing nitrile groups is acidic and, thus, can be deprotonated by the hydride ion of NaH. This results in the formation of a carbanion, which attacks the electrophilic carbon of the alkylating agent. The proposed mechanism for this reaction is shown in Figure 22.

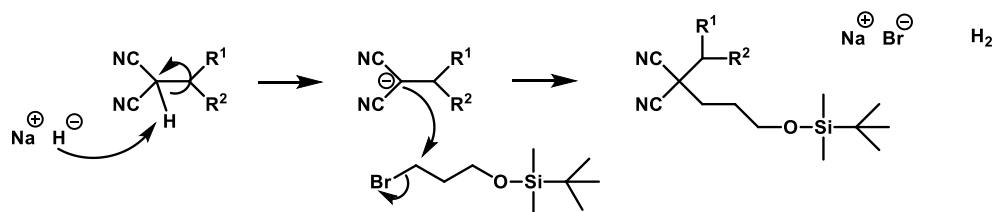


Figure 22. Proposed Mechanism for the Alkylation Reaction

Deprotection of compounds (**51**) and (**52**) was conducted using tetrabutylammonium fluoride (TBAF), a common reagent used for deprotection of silyl ether groups, to form compounds (**53**) and (**54**) in 59% and 76% yields, respectively (Figure 23). When (**51**) was deprotected, a by-product was formed that could not be isolated by column chromatography. Based on TLC analysis of every fraction collected during column purification, like fractions were combined and a sample was analyzed by GC. A 2:1 mixture of (**53**) to the unknown by-product was observed, as illustrated in the gas chromatogram (Figure 24). The yield reported for (**53**) was determined by multiplying the fractional area of its peak by the total mass of the collected fractions. A by-product was not observed for the deprotection of (**52**).

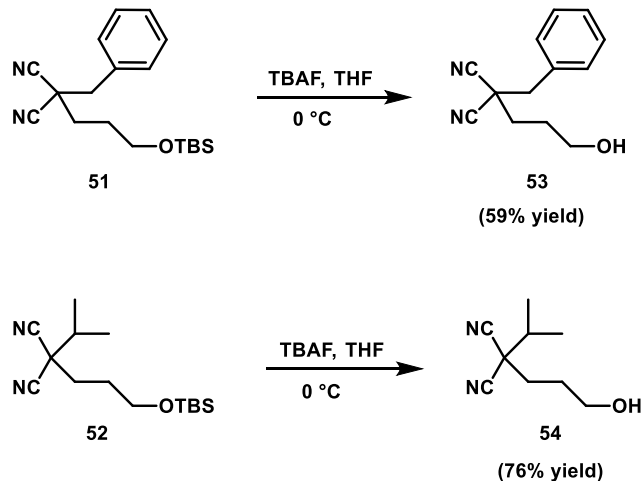


Figure 23. Deprotection of Compounds 51 and 52

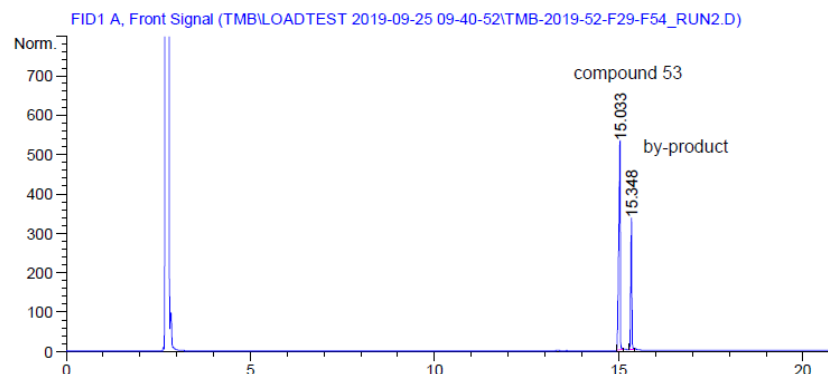


Figure 24. Gas Chromatogram of Purified Fractions for Compound 53

The fluoride ion behaves as a nucleophile and attacks the silicon atom, creating a strong covalent bond. The alkoxide ion is protonated during workup. The proposed mechanism for this reaction is shown in Figure 25.

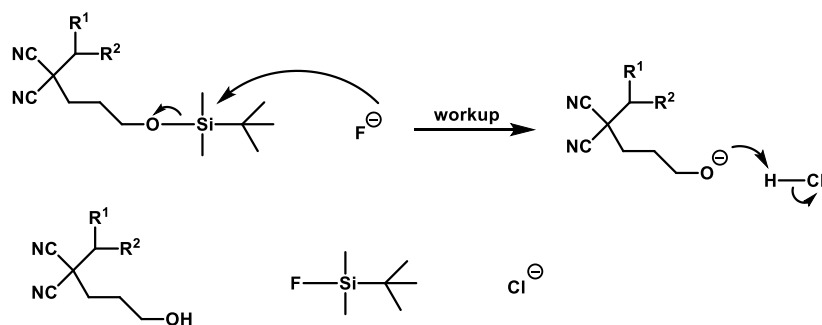


Figure 25. Proposed Mechanism for the Deprotection Reaction

2.4.4 Cyclization

The cyclization of a bifunctional chain molecule X ~ Y suffers from the competing intermolecular polymerization reaction (Figure 26). If the intramolecular cyclization is unimolecular, and thus, first-order in the substrate concentration, and the

polymerization reaction is bimolecular, and therefore second-order, then low substrate concentrations should favor the former over the latter.

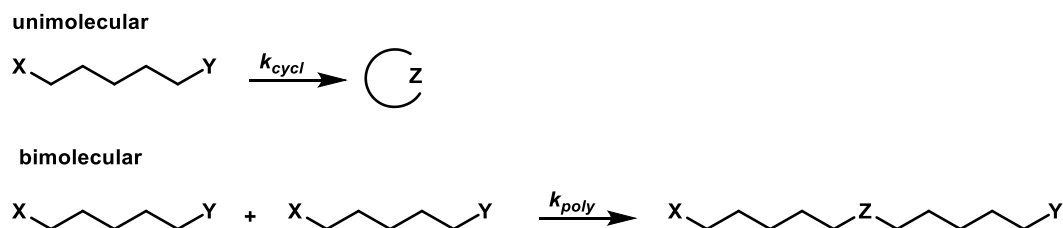


Figure 26. Simple Intramolecular and Intermolecular Reaction Kinetics

Cyclization of compounds (**53**) and (**54**) were carried out in dichloroethane (DCE) at reflux conditions, using *p*-toluenesulfonic acid monohydrate (*p*-TsOH•H₂O) as the Brønsted acid (Figure 27). Hydrates are compounds that contain water molecules as part of their crystalline structure. The water of hydration may be removed upon heating, resulting in free water molecules in solution. Thus, the intermediate iminolactones (**55**) and (**57**) hydrolyzed to generate the desired δ -lactones (**56**) and (**58**) in 64% and 74% yields, respectively.

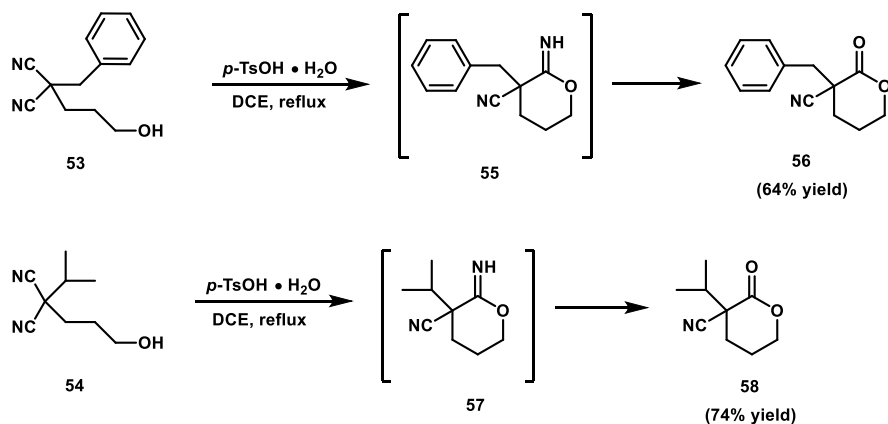


Figure 27. Intramolecular Cyclization of Compounds 53 and 54

For compound (**53**), initial concentrations of 0.050 M and 0.025 M in DCE were employed to determine the impact of the high dilution method in suppressing the formation of oligomeric products. Based on the peak percent areas of (**56**) and the by-product via GC analysis of the crude products for reactions conducted at initial concentrations of 0.050 M and 0.025 M, the relative amount of by-product reduced by 50% (Figure 28).

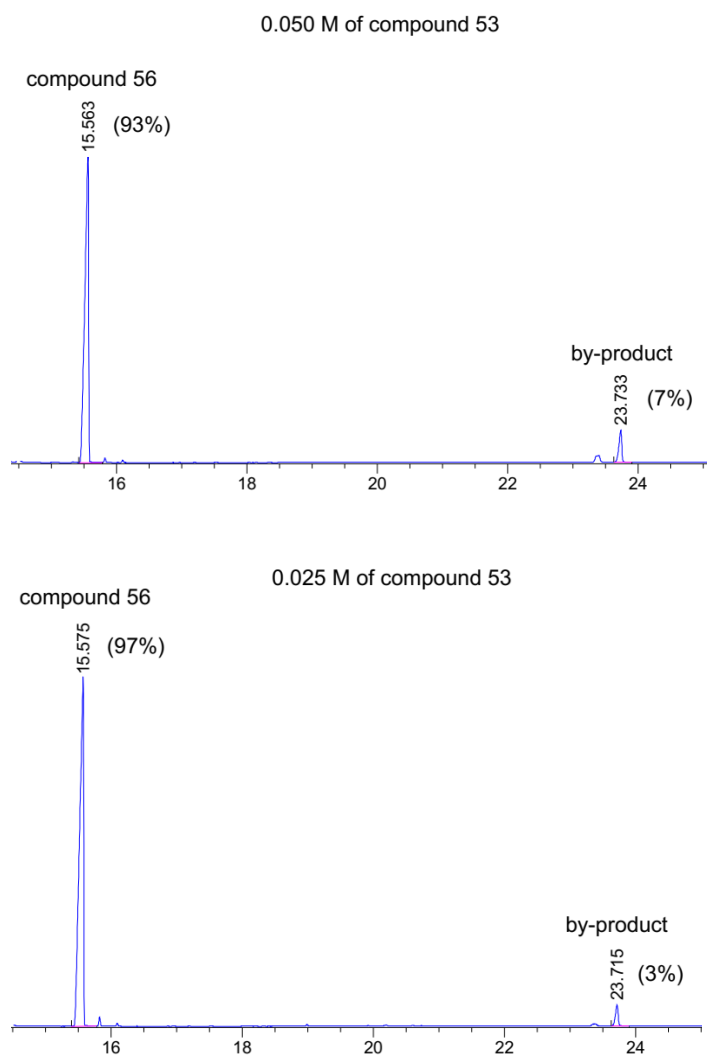


Figure 28. Gas Chromatograms of Crude Products for Compound 56

The by-product was isolated and the mass was observed - by high resolution mass spectrometry (HRMS) - to be double the mass of the desired lactone (**56**). One nitrile group of compound (**53**) could have hydrolyzed to the carboxylic acid (**59**); and, in turn, esterification of two molecules of (**59**), each containing a carboxylic acid and alcohol functionality, could form the diester (**60**) (Figure 29). The mass of by-product (**60**) ($C_{26}H_{26}N_2O_4$) is twice that of the desired δ -lactone (**56**) ($C_{13}H_{13}NO_2$). Cyclization of (**54**) was conducted at a substrate concentration of 0.025 M, in which the same dimer effect was also observed via HRMS.

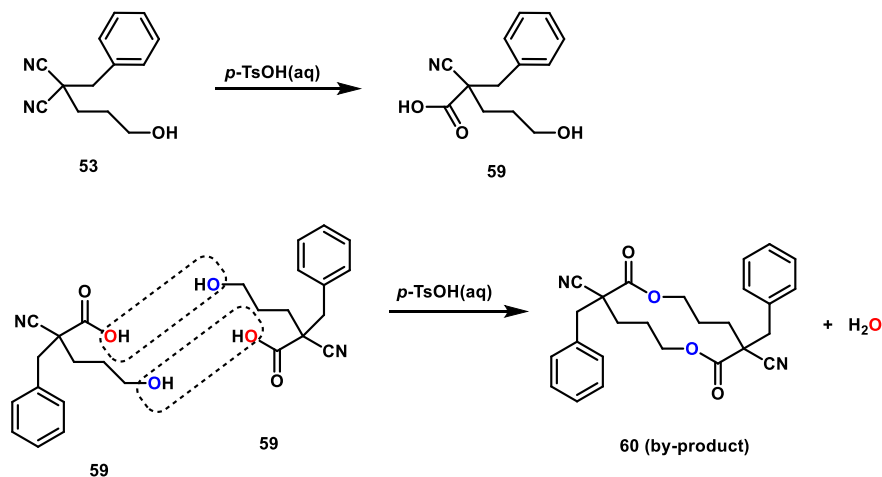


Figure 29. Acid-Catalyzed Hydrolysis and Esterification

The cyclization mechanism potentially involves the Brønsted acid behaving as a bifunctional agent, activating both the cyano and hydroxy functional groups present in the substrate. The acidic proton of the catalyst coordinates with the nitrogen atom of the nitrile and the Lewis basic oxygen coordinates with the hydrogen atom of the hydroxyl group. The electrophilic carbon atom of the nitrile group can readily undergo

nucleophilic attack by the oxygen atom of the hydroxyl group. Hydrolysis of the imino lactone intermediate generates the desired lactone. The proposed mechanism is illustrated in Figure 30.

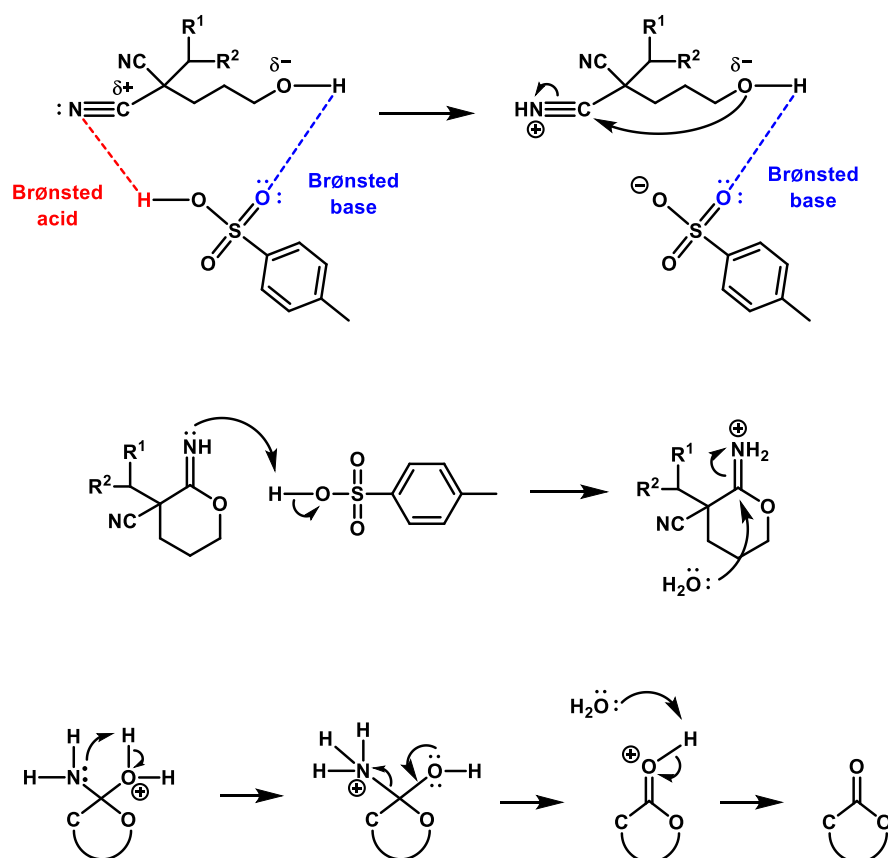


Figure 30. Proposed Mechanism for the Intramolecular Cyclization Reaction

CHAPTER III

CONCLUSION

3.1. Summary of Current Investigation

This work focused on using organocatalysis to synthesize δ -lactones. The synthetic methodology utilized the Pinner reaction to transform a hydroxynitrile into a cyclic ester. The hypothesis that a Brønsted acid behaves as a bifunctional agent, activating both the cyano and hydroxy functional groups present in the substrate resulting in an intramolecular cyclization reaction, was tested by screening two substrates containing a dinitrile group, benzylmalononitrile and isopropylmalononitrile. The desired lactones were formed in moderate yields. Diester byproducts were also generated via acid-catalyzed hydrolysis and esterification reactions; but their formation was minimized using a high dilution method to promote intramolecular cyclization over intermolecular polymerization.

3.2 Future Considerations

Efficient synthetic methodologies are of critical importance for generating chiral building blocks, as enantiomerically pure molecules are key intermediates in the synthesis of pharmaceuticals. Thus, a logical extension of this work is to synthesize six-membered ring lactones asymmetrically using a chiral Brønsted acid catalyst; and to expand the substrate scope to validate the general utility and robustness of the novel

cyclization method. Moreover, bioassays of the enantioenriched lactones is needed to gain insight about their biological activity and potential use as a drug target.

Another possible avenue to pursue is the manipulation of the remaining nitrile substituent bonded to the lactone core. As mentioned previously, the nitrile functional group can readily undergo transformations, making them key precursors towards the synthesis of complex molecules. Derivatization of the lactone products could be applicable to the generation of value-added compounds.

A paper, in collaboration with PhD student Amber Kelly, is forthcoming that will address these considerations and include work presented in this thesis.

3.3 Challenges in Organocatalysis

Organocatalysis is still in its infancy compared to metal-catalyzed processes or enzyme-mediated transformations, so there are ongoing challenges that need to be addressed. One major drawback of utilizing organocatalysts is low efficiency³³. The use of organocatalysts on an industrial scale is hampered by the need for high catalytic loading (≥ 10 mol %), long reaction times (≥ 5 hours), as well as by the difficult separation of the catalysts from products.

While new reactions are constantly being discovered, many reactions involving organocatalysis have a narrow substrate scope. Nothing is more frustrating than a failed reaction on a related substrate. One reason for this major limitation is the lack of mechanistic information of most organocatalytic reactions, specifically on experimental determination of kinetic data. Discovery of new reactions is greatly outpacing the knowledge of their underlying mechanisms. Thus, increasing mechanistic insights will

further improve the design of catalysts with better efficiency and exploit synthetic pathways.

CHAPTER IV

EXPERIMENTAL

4.1 General Information

Unless specified, all solvents and reagents were obtained from commercial sources and used as received; anhydrous solvents were dried following standard procedures. Reactions were carried out in flamed-dried glassware under an inert atmosphere of argon.

Column chromatography was performed using flash grade silica gel (particle size: 40-63 μm , 230 x 400 mesh). Analysis of fractions was conducted by thin layer chromatography using silica F254 pre-coated plates and KMnO_4 stain was used to visualize the components. Gas chromatography (GC) analysis was performed on an Agilent 7890A GC system, equipped with a flame-ionization detector. A HP-5 capillary column ((5%- phenyl)-methylpolysiloxane), 30-m length, 0.320 mm i.d., 0.25 μm thickness) was used for the separation of analytes.

The ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were obtained on a JEOL ECS 400 MHz spectrometer using CDCl_3 as the solvent at room temperature. The NMR chemical shifts (δ) are reported in ppm. Abbreviations for ^1H NMR: s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet. High resolution mass spectra (HRMS) were obtained on a LTQ Orbitrap XL in positive mode, with electrospray ionization as the ion source.

4.2 Synthesis of Compound 46

To a mixture of dicyanoalkene (**45**) (2.00 g, 13.0 mmol) in ethanol (150 mL) at 0 °C, NaBH₄ (491, mg, 13.0 mmol) was added portionwise. After stirring for 1 h, the reaction mixture was neutralized with 5 M aqueous HCl solution to pH ~ 6 and extracted with diethyl ether (3 x 100 mL). The extract was dried over Na₂SO₄, filtered, and concentrated to afford (**46**) as a white solid (1.88 g, 93% yield). ¹H NMR (400 MHz, CDCl₃): δ = 7.36 (m, 5 H), 3.90 (t, *J* = 7.0 Hz, 1 H), 3.28 (d, *J* = 7.0 Hz, 2 H). ¹³C NMR (100 MHz, CDCl₃): δ = 133.0, 129.4, 129.2, 129.0, 112.2, 36.8, 25.1. Spectra data matches previously reported data³².

4.3 Synthesis of Compound 48

To a solution of dicyanoalkene (**47**) (0.80 mL, 7.9 mmol) in ethanol (150 mL) at 0 °C, NaBH₄ (297 mg, 7.85 mmol) was added portionwise. After 1 h of stirring, the reaction mixture was neutralized with 5 M aqueous HCl solution to pH ~ 6 and extracted with CH₂Cl₂ (3 x 80 mL). The extract was dried over Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by column chromatography with ethyl acetate/hexane (0% to 10% ethyl acetate) to give (**48**) as a clear oil (462 mg, 54% yield). ¹H NMR (400 MHz, CDCl₃): δ = 3.57 (d, *J* = 5.5 Hz, 1 H), 2.36 (m, 1 H), 1.24 (d, *J* = 6.8 Hz, 6 H). ¹³C NMR (100 MHz, CDCl₃): δ = 112.0, 31.3, 30.5, 19.6. Spectra data matches previously reported data³¹.

4.4 Synthesis of Compound 50

To a solution of 3-bromo-1-propanol (**49**) (1.00, mL, 10.6 mmol) in CH₂Cl₂ (11 mL) at 0 °C, imidazole (1.40 g, 21.2 mmol) then TBSCl (2.40 g, 15.9 mmol) were added.

After stirring overnight, the reaction mixture was neutralized with saturated aqueous NH_4Cl solution (15 mL) and extracted with CH_2Cl_2 (3 x 12 mL). The extract was dried over Na_2SO_4 , filtered, and concentrated under vacuum to generate (**50**) as a clear oil (2.72 g, 100% yield). ^1H NMR (400 MHz, CDCl_3): δ = 3.72 (t, J = 5.7 Hz, 2 H), 3.50 (t, J = 6.4 Hz, 2 H), 2.02 (m, 2 H), 0.88 (s, 9 H), 0.05 (s, 6 H). ^{13}C NMR (100 MHz, CDCl_3): δ = 60.5, 35.6, 30.8, 26.0, 18.4, -5.3. Spectra data matches previously reported data³⁴.

4.5 Synthesis of Compound 51

To a mixture of NaH (60% dispersion, 0.51 g, 13 mmol) in DMF (64 mL) at 0 °C, (**46**) (6.40 mmol, 1.00 g) followed by (**50**) (3.24 g, 12.8 mmol) were added. After stirring overnight, the reaction mixture was neutralized with 5 M aqueous HCl solution to pH ~ 6. The contents were transferred to a large separatory funnel, to which 320 mL deionized H_2O was added. The reaction mixture was extracted with CH_2Cl_2 (3 x 80 mL), dried over Na_2SO_4 , filtered, and concentrated under vacuum. The residue was purified by column chromatography with ethyl acetate/hexane (3% to 10% ethyl acetate) to generate (**51**) as a white solid (839 mg, 40% yield). ^1H NMR (400 MHz, CDCl_3): δ = 7.38 (m, 5 H), 3.69 (t, J = 5.6 Hz, 2 H), 3.21 (s, 2 H), 2.05 (m, 2 H), 1.90 (m, 2 H), 0.86 (s, 9 H), 0.03 (s, 6 H). ^{13}C NMR (100 MHz, CDCl_3): δ = 132.1, 130.3, 129.0, 128.9, 115.4, 61.4, 43.5, 39.2, 34.5, 28.9, 26.0, 18.3, -5.3. HRMS (ESI): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{28}\text{N}_2\text{OSi}$: 329.20437; found: 329.20401. mp = 59.4 °C to 63.4 °C.

4.6 Synthesis of Compound 52

To a mixture of NaH (60% dispersion, 0.25 g, 6.5 mmol) in DMF (42 mL) at 0 °C, (**48**) (445 mg, 4.11 mmol) followed by (**50**) (2.08 g, 8.22 mmol) were added. After

stirring overnight, the reaction mixture was neutralized with 5 M aqueous HCl solution to pH ~ 6. The contents were transferred to a large separatory funnel, to which 300 mL deionized H₂O was added. The reaction mixture was extracted with CH₂Cl₂ (3 x 60 mL), dried over Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by column chromatography with ethyl acetate/hexane (0% to 3% ethyl acetate) to form (**52**) as a clear oil (548 mg, 47% yield). ¹H NMR (400 MHz, CDCl₃): δ = 3.70 (t, *J* = 5.6 Hz, 2 H), 2.17 (m, 1 H), 2.01 (m, 2 H), 1.86 (m, 2 H), 1.23 (d, *J* = 6.7 Hz, 6 H), 0.88 (s, 9 H), 0.05 (s, 6 H). ¹³C NMR (100 MHz, CDCl₃): δ = 115.3, 61.5, 43.7, 35.5, 32.3, 29.0, 25.9, 18.4, -5.3. HRMS (ESI): *m/z* [M + H]⁺ calcd for C₁₅H₂₈N₂OSi: 281.20437; found: 281.20425.

4.7 Synthesis of Compound 53

To a 1 M solution of TBAF (2.00 mL, 2.00 mmol) in THF at 0 °C, a cold solution of (**51**) (385 mg, 1.00 mmol) in THF (11 mL) was added. After stirring for 90 min, the reaction was neutralized with 5 M aqueous HCl solution to pH ~ 6. The contents were transferred to a separatory funnel, to which 60 mL deionized H₂O was added. The reaction mixture was extracted with CH₂Cl₂ (3 x 25 mL), dried over Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by column chromatography with ethyl acetate/hexane (20% to 30% ethyl acetate) to afford **53** as a clear oil (131 mg, 59%). ¹H NMR (400 MHz, CDCl₃): δ = 7.38 (m, 5 H), 3.77 (m, 2 H), 3.22 (s, 2 H), 2.11 (m, 2 H), 1.96 (m, 2 H). ¹³C NMR (100 MHz, CDCl₃): δ = 132.0, 130.3, 129.1, 128.9, 115.3, 61.2, 43.6, 39.3, 34.4, 28.7. HRMS (ESI): *m/z* [M + H]⁺ calcd for C₁₃H₁₄N₂O: 215.1179; found: 215.1178.

4.8 Synthesis of Compound 54

To a solution of **52** (609 mg, 2.17 mmol) in THF (22 mL) at 0 °C, a 1 M solution of TBAF (4.34 mL, 4.34 mmol) in THF was added. After stirring for 90 min, the reaction was neutralized with 5 M aqueous HCl solution to pH ~ 6. The contents were transferred to a separatory funnel, to which 100 mL deionized H₂O was added. The reaction mixture was extracted with CH₂Cl₂ (3 x 25 mL), dried over Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by column chromatography with ethyl acetate/hexane (40% to 60% ethyl acetate) to afford (**54**) as a clear oil (273 mg, 76%). ¹H NMR (400 MHz, CDCl₃): δ = 3.78 (m, 2 H), 2.18 (m, 1 H), 2.05 (m, 2 H), 1.93 (m, 2 H), 1.24 (d, *J* = 6.7 Hz, 6 H). ¹³C NMR (100 MHz, CDCl₃): δ = 115.2, 61.4, 43.8, 35.8, 32.2, 28.9, 18.4. HRMS (ESI): *m/z* [M + H]⁺ calcd for C₉H₁₃N₂O: 167.11789; found: 167.11748.

4.9 Synthesis of Compound 56

To *p*-TsOH•H₂O (148 mg, 0.780 mmol) at 80 °C was added a solution of compound (**53**) (119 mg, 0.390 mmol) in DCE (15.6 mL). After stirring for 90 mins, the reaction mixture was quenched with 16 mL of deionized H₂O. The reaction mixture was extracted with CH₂Cl₂ (3 x 16 mL), dried over Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by column chromatography with ethyl acetate/hexane (15% ethyl acetate) to give (**56**) as a white solid (53.6 mg, 64%). ¹H NMR (400 MHz, CDCl₃): δ = 7.31 (m, 5 H), 4.52 (m, 1 H), 4.29 (m, 1 H), 3.44 (d, *J* = 13.8 Hz, 1 H), 3.25 (d, *J* = 13.9 Hz, 1 H), 2.11 (m, 2 H), 1.95 (m, 2 H). ¹³C NMR (100 MHz, CDCl₃): δ =

165.5, 133.4, 130.5, 128.9, 128.2, 118.9, 70.6, 44.7, 42.1, 29.4, 20.0. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{13}H_{13}NO_2$: 238.0839; found: 238.0837. mp = 83.4 °C to 86.3 °C.

4.10 Synthesis of Compound 58

To p -TsOH•H₂O (289 mg, 1.52 mmol) at 80 °C was added a solution of compound (**54**) (126 mg, 0.760 mmol) in DCE (30.4 mL). After stirring for 90 mins, the reaction mixture was quenched with 30 mL of deionized H₂O. The reaction mixture was extracted with CH₂Cl₂ (3 x 16 mL), dried over Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by column chromatography with ethyl acetate/hexane (10% to 25% ethyl acetate) to give (**58**) as a clear oil (93.1 mg, 74%). ¹H NMR (400 MHz, CDCl₃): δ = 4.55 (m, 1 H), 4.34 (m, 1 H), 2.61 (sept, 1 H), 2.27-1.95 (m, 4 H), 1.16 (d, J = 7.0 Hz, 3 H), 1.03 (d, J = 6.7 Hz, 3 H). ¹³C NMR (100 MHz, CDCl₃): δ = 165.6, 119.2, 70.5, 49.0, 34.2, 26.2, 20.4, 17.8, 17.5. HRMS (ESI): m/z $[M + H]^+$ calcd for C₉H₁₃NO₂: 168.10191; found: 168.10151.

BIBLIOGRAPHY

1. Knoevenagel, E., The Preparation of Benzylidene Acetoacetic Esters. *Ber. Dtsch. Chem. Ges.* **1896**, 29, 172-174.
2. Hajos, Z. G.; Parrish, D. R., Asymmetric Synthesis of Bicyclic Intermediates of Natural Product Chemistry. *J. Org. Chem.* **1974**, 39 (12), 1615-1621.
3. Eder, U.; Sauer, G.; Wiechert, R., New Type of Asymmetric Cyclization to Optically Active Steroid CD Partial Structures. *Angew. Chem. Int. Ed.* **1971**, 10 (7), 496-497.
4. List, B.; Lerner, R. A.; III, C. F. B., Proline-Catalyzed Direct Asymmetric Aldol Reactions. *J. Am. Chem. Soc.* **2000**, 122 (10), 2395-2396.
5. Bahmanyar, S.; Houk, K. N., Transition States of Amine-Catalyzed Aldol Reactions Involving Enamine Intermediates: Theoretical Studies of Mechanism, Reactivity, and Stereoselectivity. *J. Am. Chem. Soc.* **2001**, 123 (45), 11273-11283.
6. Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, B., Quantum Mechanical Predictions of the Stereoselectivities of Proline-Catalyzed Asymmetric Intermolecular Aldol Reactions. *J. Am. Chem. Soc.* **2003**, 125 (9), 2475-2479.
7. Alexakis, A.; Andrey, O., Diamine-Catalyzed Asymmetric Michael Additions of Aldehydes and Ketones to Nitrostyrene. *Org. Lett.* **2002**, 4 (21), 3611-3614.
8. List, B.; Pojarliev, P.; Martin, H. J., Efficient Proline-Catalyzed Michael Additions of Unmodified Ketones to Nitro Olefins. *Org. Lett.* **2001**, 3 (16), 2423-2425.
9. Hayashi, Y.; Tsuboi, W.; Itaru Ashimine; Urushima, T.; Shoji, M.; Sakai, K., The Direct and Enantioselective, One-Pot, ThreeComponent, Cross-Mannich Reaction of Aldehydes. *Angew. Chem. Int. Ed.* **2003**, 42 (31), 3677-3680.
10. List, B., The Direct Catalytic Asymmetric Three-Component Mannich Reaction. *J. Am. Chem. Soc.* **2000**, 122 (38), 9336-9337

11. Bøgevig, A.; Juhl, K.; Kumaragurubaran, N.; Zhuang, W.; Jørgensen, K. A., Direct Organo-Catalytic Asymmetric α -Amination of Aldehydes: A Simple Approach to Optically Active α -Amino Aldehydes, α -Amino Alcohols, and α -Amino Acids. *Angew. Chem. Int. Ed.* **2002**, *41* (10), 1790-1793.
12. Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bøgevig, A.; Jørgensen, K. A., Direct L-Proline-Catalyzed Asymmetric α -Amination of Ketones. *J. Am. Chem. Soc.* **2002**, *124* (22), 6254-6255.
13. Vignola, N.; List, B., Catalytic Asymmetric Intramolecular α -Alkylation of Aldehydes. *J. Am. Chem. Soc.* **2004**, *126* (2), 450-451.
14. Pellissier, H., *Recent Developments in Asymmetric Organocatalysis*. RSC: Cambridge, 2010.
15. Akiyama, T.; Mori, K., Stronger Brønsted Acids: Recent Progress. *Chem. Rev.* **2015**, *115* (17), 9277-9306.
16. Akiyama, T.; Junji Itoh, K. Y.; Fuchibe, K., Enantioselective Mannich-Type Reaction Catalyzed by a Chiral Brønsted Acid. *Angew. Chem. Int. Ed.* **2004**, *43* (12), 1566-1568.
17. Uraguchi, D.; Terada, M., Chiral Brønsted Acid-Catalyzed Direct Mannich Reactions via Electrophilic Activation. *J. Am. Chem. Soc.* **2004**, *126* (17), 5356-5357.
18. Kampen, D.; Reisinger, C. M.; List, B., Chiral Brønsted Acids for Asymmetric Organocatalysis. *Top. Curr. Chem.* **2010**, *291*, 395-456.
19. Gilchrist, T. L., *Heterocyclic Chemistry*. Pitman Publishing: London, England, 1985.
20. Cossy, J., *Synthesis of Saturated Oxygenated Heterocycles I*. Springer: Heidelberg, 2014; Vol. I.
21. Potmesil, M.; Pinedo, H., *Camptothecins: New Anticancer Agents*. CRC Press: Boca Raton, FL, 1995.
22. Legarza, K.; Yang, L.-X., Novel Camptothecin Derivatives. *In Vivo* **2005**, *19* (1), 283-292.

23. P.Money, N., Fungi and Biotechnology. In *The Fungi*, Watkinson, S. C.; Boddy, L.; Money, N. P., Eds. Academic Press: Cambridge, Massachusetts, 2015.
24. Elgazwy, A.-S. S. H.; Refaee, M. R. M., The Chemistry of Alkenyl Nitriles and its Utility in Heterocyclic Synthesis. *Organic Chem. Curr. Res.* **2013**, 2 (2), 117-143.
25. Abdelrazek, F. M.; Bahbouh, M. S., Recent Advances in the Chemistry of Nitriles and Enaminonitriles. *Jordan J. Earth Environ. Sci.* **2012**, 4 (1), 47-61.
26. Paryzek, Z.; Skiera, I., Synthesis and Cleavage of Lactones and Thiolactones. Applications in Organic Synthesis: A Review. *Org Prep Proced Int* **2007**, 39 (3), 203-296.
27. Pinner, A.; Klein, F., The Conversion of Nitriles to Imides. *Ber. Dtsch. Chem. Ges.* **1878**, 11, 1475-1487.
28. Kula, J.; Sikora, M.; Sadowska, H.; Piwowarski, J., Short Synthetic Route to the Enantiomerically Pure (*R*)-(+)- γ -Decalactone. *Tetrahedron* **1996**, 52 (34), 11321-11324.
29. Aplander, K.; Hidestøl, O.; Katebzadeh, K.; Lindström, U. M., A Green and Facile Route to γ - and δ -lactones via Efficient Pinner-Cyclization of Hydroxynitriles in Water. *Green Chem.* **2005**, 8 (1), 22-24.
30. Zhang, X.; Jia, X.; Liu, N.; Guo, X.; Song, Y.; Fan, X., 5-Hydroxypent-2-enenitriles as Precursors toward Dihydropyranones, Dienenitriles and Functionalized Naphthalenes. *Tetrahedron* **2013**, 69 (26), 5374-5382.
31. Sammelson, R. E.; Allen, M. J., A Convenient and Selective One-Pot Method for the Synthesis of Monosubstituted Secondary Alkyl Malononitriles. *Synthesis* **2005**, 2005 (4), 543-546.
32. Tayyari, F.; Wood, D. E.; Fanwick, P. E.; Sammelson, R. E., Monosubstituted Malononitrile: Efficient One-Pot Reductive Alkylations of Malononitrile with Aromatic Aldehydes. *Synthesis* **2008**, 2008 (2), 279-285.
33. Zhou, Q.-L., Transition-Metal Catalysis and Organocatalysis: Where Can Progress Be Expected? *Angew. Chem. Int. Ed.* **2016**, 55, 5352-5353.

34. Maeda, Y.; Saito, K.; Akamatsu, N.; Chiba, Y.; Ohno, S.; Okui, Y.; Yamada, M.; Hasegawa, T.; Kako, M.; Akasaka, T., Analysis of Functionalization Degree of Single-Walled Carbon Nanotubes Having Various Substituents. *J. Am. Chem. Soc.* **2012**, *134*, 18101-18108.

APPENDIX A

NMR SPECTRA

The ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were plotted on a JEOL ECS 400 MHz spectrometer using CDCl_3 as a solvent at room temperature. The NMR chemical shifts (δ) are reported in ppm. Abbreviations for ^1H NMR: s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet.

